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## RESEARCH ARTICLE

# THE EXPANDING COHORT OF ASPERGILLOSIS AND MIXED FUNGAL INFECTIONS IN COVID 19 PANDEMIC: OUR EXPERIENCE

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### ABSTRACT

**Introduction-**This study is aimed to present the clinical features, incidence, associated complications and management strategies in post Covid aspergillosis and mixed fungal infections at a tertiary health care setup. The development of Aspergillosis in Post Covid patients is a novel presentation of the fungus and with the advent of new data, our horizons regarding the association of Aspergillosis and Covid is ever expanding. Currently, the causation of invasive fungal sinusitis in the form of Mucormycosis has been well documented. However, with new data and going by the fungal culture reports, the incidence of mixed fungal infections and aspergillosis has not been well studied, and the clinical features and management strategies is an evolving spectrum on which we plan to shed some light. **Materials and Methods-** This is an observational prospective study conducted by us at a Tertiary Health Set up where patients presented with complains of nasal pain, facial pain, ptosis, proptosis, facial asymmetry and with scans suggestive of sinusitis with history of Covid, and clinical suspicion of invasive fungal sinusitis were evaluated. Subsequently, nasal crusts were sent for KOH and Fungal culture. After reviewing of the scans and evaluating the KOH report, these patients were posted for endoscopic sinus surgery with debridement. **Conclusion-** Thus, Aspergillosis should also be a cause for suspicion especially in post Covid patients, as a reason for invasive fungal sinusitis. Early treatment can help in early recovery and less morbidity, a direct association has been detected with Diabetes Mellitus and Aspergillosis, thus controlling blood sugar levels is of utmost importance in the management of these patients. Incessant use of steroids should be avoided as it is a significant risk factor in the development of post Covid Aspergillosis could not be derived.

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## INTRODUCTION

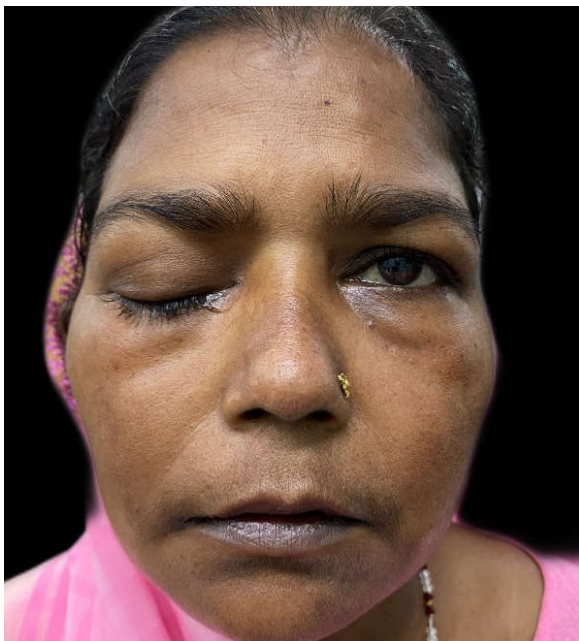
The ubiquitous fungus, Aspergillosis has been known for its wide range of infections it causes in the nose and Paranasal sinuses, ranging from fungal ball to its possible role in Allergic fungal rhino sinusitis to the extremely debilitating infection of invasive aspergillosis. Aspergillosis has been known to add brunt to the lives of people suffering from hematological malignancies, people on chemotherapy and other forms of immunosuppression. However, the development of Aspergillosis in Post Covid patients is a novel presentation of the fungus and with the advent of new data, our horizons regarding the association of Aspergillosis and Covid is ever expanding.

Many of the patients who were suffering from Covid have received a prolonged and high dosage of steroids which in turn causes immunosuppressant and makes the patient prone for the development of Aspergillosis. Not only this, immunomodulatory drugs such as Tocilizumab has been implicated in the causation of this infection. Some of these critical patients are already diabetics, and the use of steroids worsens their condition. There have been reports that hyperferritinemia in Covid patients provides an optimal breeding ground for Aspergillosis infections. Some reports also suggest that Covid may cause inflammation of the beta cells of the pancreas which can also be causative factors. All of these mechanisms can be additive and create a scenario for invasive sinusitis in such debilitated patients.

Currently, the causation of invasive fungal sinusitis in the form of Mucormycosis has been well documented. However, with new data and going by the fungal culture reports, the incidence of mixed fungal infections and aspergillosis has not been well studied, and the clinical features and management strategies is an evolving spectrum on which we plan to shed some light.

## MATERIALS AND METHODS

This is an observational prospective study conducted by us at a Tertiary Health Set up where patients who presented to the Emergency Department with complains of nasal pain, facial pain, ptosis, proptosis, facial asymmetry and with scans suggestive of sinusitis with history of Covid, and clinical suspicion of invasive fungal sinusitis were evaluated.

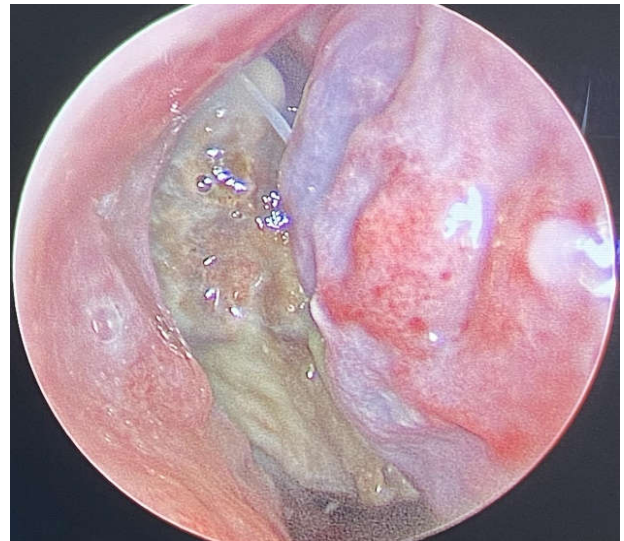


**Fig 1. Clinical picture with Right Ptosis and Proptosis and facial swelling (Patient's consent for picture has been taken)**



**Fig. 2. T2 weighted MRI of one of the other patients showing bilateral maxillary and left anterior ethmoid sinusitis and black turbinate sign on the right side**

Subsequently, nasal crusts were sent for KOH and Fungal culture. After reviewing of the scans and evaluating the KOH report, these patients were posted for endoscopic sinus surgery with debridement.

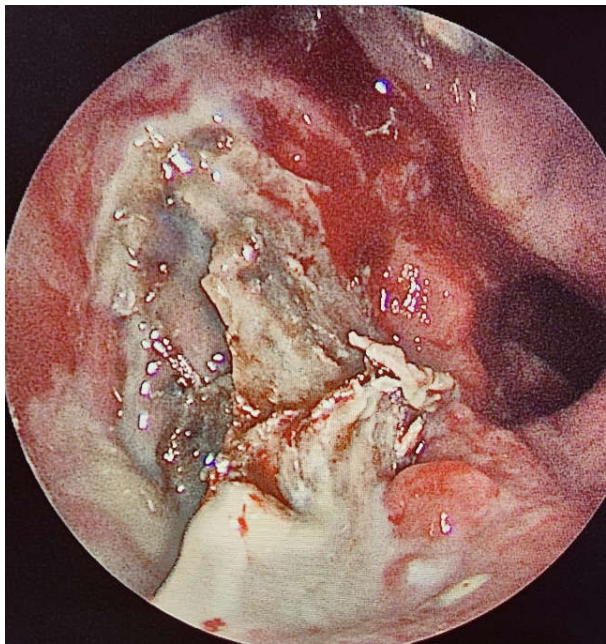


**Fig 3. Endoscopic view of fungal crusts**

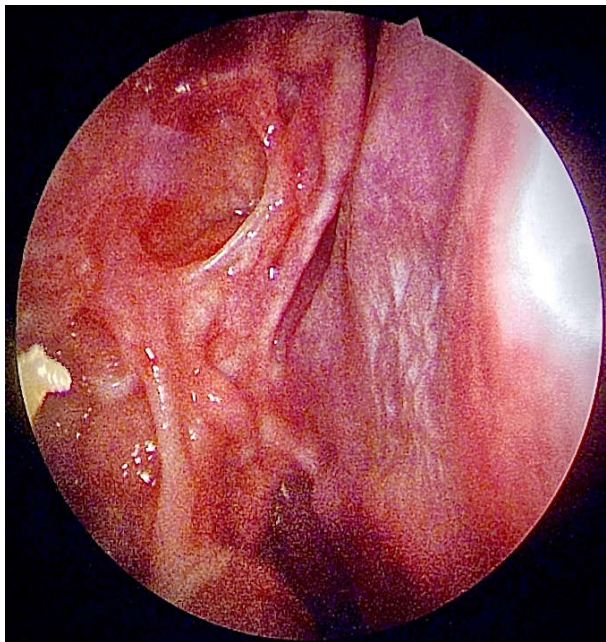
They were started empirically on Amphotericin (Conventional/Liposomal): Conventional-0.5 to 1mg/kg, Liposomal Ampho- 4 to 5mg/kg. Patients having aspergillosis on fungal culture/histopathology were started on a loading dose of Voriconazole of 400mg twice a day on the first day followed by 200mg twice a day on the remaining days for a period of 6-8 weeks. Patients who had mixed infections were started on Amphotericin and Voriconazole, and then discharged on Posaconazole and Voriconazole. Patients with palatal involvement underwent palatal debridement followed by obturator fitting. Patients with intraorbital extension were managed with transcutaneous retroorbital injection of Amphotericin B. Some of the patients underwent enucleation and exenteration of eyeball as deemed fit by the Ophthalmology Department. Patients having intracranial abscesses were drained by the neurosurgery department, and for cavernous sinus extension, major vessel thrombosis and pachymeningeal enhancement conservative management was the cornerstone in the treatments. Patients having dental loosening underwent dental extraction and debridement of necrotic bone. After doing functional endoscopic sinus surgery, patients were regularly assessed using nasal endoscopy and residual disease was removed. Patients were started on nasal spray for douching, and after completion of medical line of management and healthy mucosa on endoscopy, patients were subsequently discharged and were asked to follow up every three weeks with repeat scans, and if suspicious were again posted for endoscopy and if any residual disease present, it was removed in the same sitting.

## RESULTS

In our centre, most of the patients who presented were male in the age group of 40-60. Majority had history of diabetes which is a significant association. The most commonly involved sinus was maxillary sinus. 80 percent had orbital involvement, 45 percent had intracranial involvement and 10percent had palatal involvement. Out of the patients, 90 percent recovered and 30 percent had some morbidity in the form of loss of vision or palatal perforation.

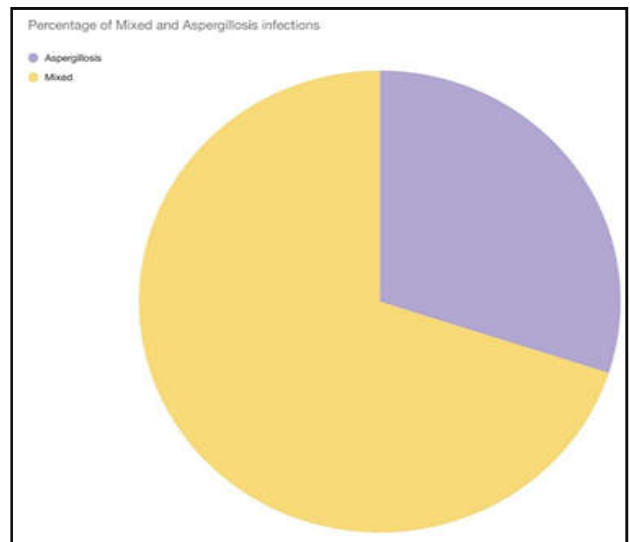


**Fig 4. Fungal crusts on repeat debridement**

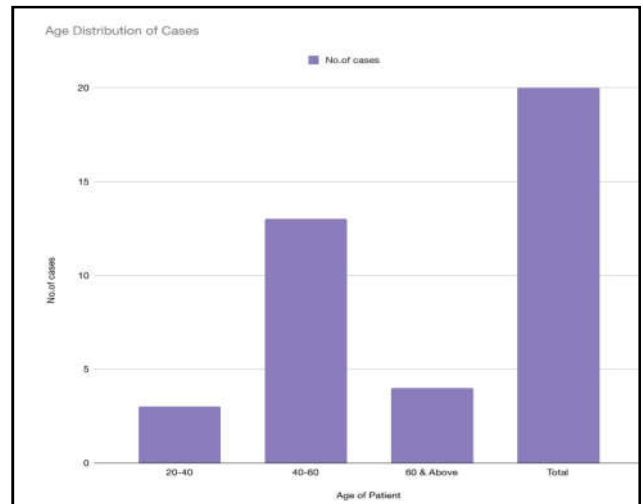


**Fig 5. Post operative endoscopy after discharge**

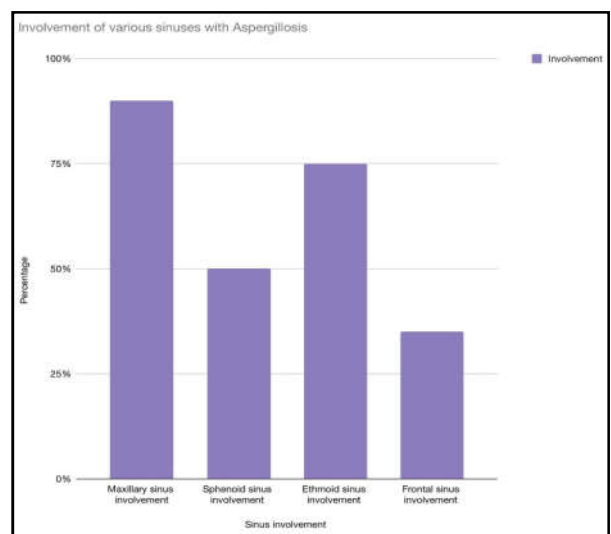
Out of the 90 patients that were operated by our unit at our tertiary level centre, a total of 20 patients were detected to have Aspergillosis infection, an incidence rate of 22.23 percentages. Out of these cases 30 percent had pure aspergillosis infection and 70 percent had a mixed infection. (Fig.6). Fig 6: Pie chart depicting percentage of mixed infections (Aspergillosis with Mucor) and pure Aspergillosis. In our centre, 85 patients were male and 15 percent were female with a sex ratio of 6:1. ( Fig.7). Around 65 percent of patients were of the age group 40 to 60. 15 percent of the patients were below 40 and 20 percent of them were above 60. Of all the patients, 70 percent had history of Diabetes Mellitus and were on treatment for the same. 20 percent of the patients had Hypertension, 15 percent had other comorbidities like hypothyroidism, ischemic heart disease and stroke. Also, 20 percent of the patients had no comorbidities. Out of all the patients, 85 percent had history of steroid use, making it a significant factor in the development of Post Covid Aspergillosis.



**Fig 6: Pie chart depicting percentage of mixed infections (Aspergillosis with Mucor) and pure Aspergillosis**



**Fig 7. Age distribution of the disease**



**Fig 8. Frequency of involvement of sinuses**

40 percent of the patients had history of oxygen use during admission For Covid 19 infection.

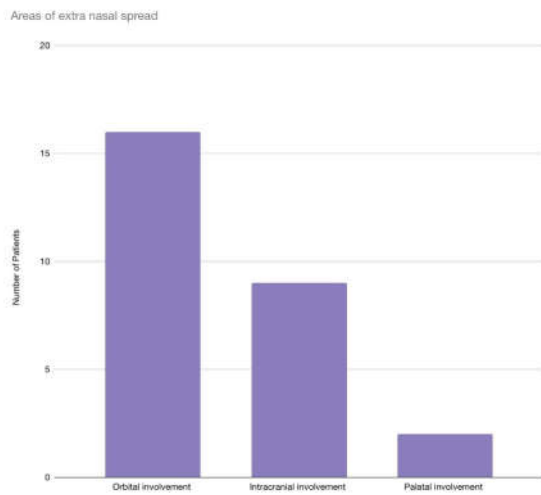


Fig. 9. Spread of the Disease (Extra-nasal involvement)



Fig. 10. Palatal Prosthesis

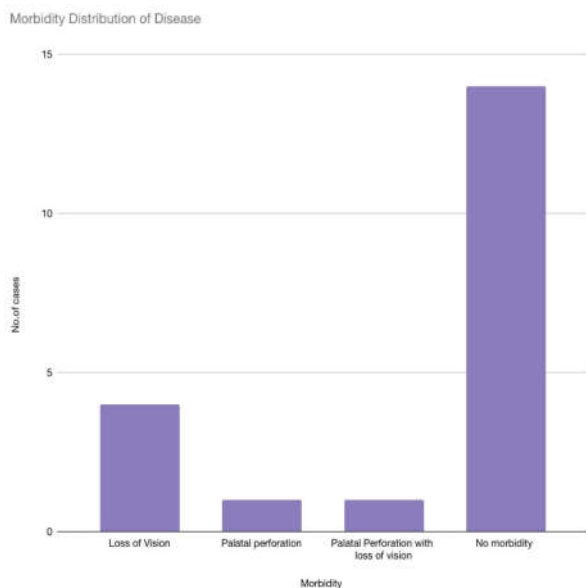


Fig 11. Morbidity Data

In all the patients, that we operated 90 percent of the patients had involvement of the maxillary sinus, 75percent had involvement of the ethmoids (anterior and posterior), 50 percent had involvement of sphenoid sinus and only 35% had involvement of frontal sinus (Fig.8).

Apart from the sinuses, 80 percent had involvement of the orbit in the form of extraconal or intraconal involvement. 45 percent of the patients had intracranial involvement in the form of pachymeningeal enhancement or in severe cases occlusion of the cerebral arteries, (Fig.9). 10 percent of these patients had palatal erosion which was debrided until healthy and then obturator was placed for these patients, (Fig.10) Out of all the patients, 20 percent had loss of vision. Out of these 80 percent were given Transcutaneous Retrorbital Amphotericin B (TRAMB) and 20 percent underwent enucleation of the eye. One patient had both palatal perforation and vision loss, (Fig.11). Out of all the patients, 90 recovered with concomitant debridement and intravenous Liposomal Amphotericin B given at our centre at 300mg/day. Patients with Paranasal sinuses involvement were given cumulative dose up to 2g. Patients with intraorbital and intracranial involvement were given cumulative dose upto 3-4g, depending on the clinical improvement and resolution of infection on repeated imaging and nasal endoscopies, after confirmation of Aspergillosis; they were also started on 400mg of Voriconazole on Day one followed by 200mg daily. In mixed infections, they were started on Posaconazole 300mg daily after completion of Amphotericin dose. However, 10 percent of the patients succumbed to the disease. The reason for this can be multifactorial. However, no statistical causation could be derived. The patients presented to us late and had significant and extensive disease burden at presentation. One of the patients had bilateral orbital involvement with loss of vision and significant intracranial involvement with thrombosis of cavernous sinus and of the anterior and middle cerebral artery. The other patient had history of ischemic heart disease and stroke. Both of these patients had Diabetes as well.

## DISCUSSION

The prevalence of fungal sinus disease is thought to be have been increasing in recent decades There is speculation that this may be due to increased awareness, antibiotic overuse and increased use of immunosuppressant medications<sup>(1)</sup> The most commonly encountered fungal species in medical practice are Candida species and Aspergillus species<sup>(2)</sup>. The less commonly encountered, but known for their invasive potential, are fungi of the Zygomycota order (Mucor, Rhizopus, Apophysomyces et al.). These fungi are often implicated in immunocompromised individuals, as in the case of Mucormycosis<sup>(1)</sup>. This condition is characterised by the presence of hyphal invasion of sinus tissue and a time course of less than 4 weeks<sup>(5, 6)</sup>. AIFR (Acute Invasive Fungal Sinusitis) is most commonly encountered in those patients with a form of immunocompromise. Due to immunosuppression, the diagnosis can be difficult due to inability to mount an immune response<sup>(7)</sup>. Such patients broadly fall into two categories and each of these have commonly associated pathogens with them. The first are diabetic patients (roughly 50%), particularly if poorly controlled, and is frequently associated with diabetic ketoacidosis. This subset of patients frequently has Zygomycetes order isolated<sup>(3)</sup>. This is due to their affinity for acidotic environments with high glucose concentrations. The second subset of patients is those who are immunosuppressed—for example, with neutropenia, HIV/AIDS, hematological malignancies and patients receiving chemotherapy Symptoms like crusting in nose, epistaxis, headache and fever are commonly reported<sup>(8)</sup>. Usually fever of unknown origin which has failed to respond after 48 hours of broad spectrum antibiotics maybe the initial symptom<sup>(9)</sup>.

In early stages, mild discoloration, granulation and ulceration are present <sup>(10)</sup>. Recent introduction of serial Aspergillus galactomannan antigen test may provide early evidence of IFS<sup>(3)</sup>. Histologically, AIFRS is defined by fungal forms invading into the submucosal tissue, often associated with angioinvasion resulting in vascular thrombosis, infarction, and necrosis <sup>(4)</sup>. Rapid diagnosis is critical because fungal forms may grow into vital structures, including the orbit and cranial cavity, and patients with involvement of these structures have a significantly high mortality rate <sup>(5)</sup>. Invasive fungal sinusitis has more bony erosion and more extra sinus diseases with intraorbital and intracranial involvement <sup>(11)</sup>. Without prompt treatment, there is chance of rapid disease progression with mortality in the range of 50-80 percent from intraorbital and intracranial extension <sup>(9)</sup>. Surgery is important for providing tissue culture, reducing disease burden and allowing recovery of the bone marrow <sup>(9)</sup>. There also appears to be an additional small subset of patients with a propensity to develop AIFR. These are those who are iron overloaded or in renal failure and receiving deferoxamine for iron chelation. The mechanism behind this is that some fungi (Rhizopus) can bind to deferoxamine <sup>(1)</sup>. However with Covid we are eyeing this presentation now in Covid and post Covid patients. This has been speculated to be due to underlying diabetes, excessive use of steroids causing immunosuppression, hyperferritinemia and high IL 6 levels. However, it is the result of play of many of these factors, some of which we will study here.

## CONCLUSION

- Thus, Aspergillosis should also be a cause for suspicion especially in post Covid patients, as a reason for invasive fungal sinusitis.
- Early treatment can help in early recovery and less morbidity, and with increasing involvement of the brain and orbit, the survival chances reduce significantly.
- A direct association has been detected with Diabetes Mellitus and Aspergillosis, thus controlling blood sugar levels is of utmost importance in the management of these patients apart from reducing the fungal load.
- Incessant use of steroids should be avoided as it is a significant risk factor in the development of post Covid Aspergillosis could not be derived.
- More research is needed to look for other factors that might be contributing to the disease, whether improving immunity helps in disease control and if prophylaxis can be instituted for high risk patients.

**Conflict of interest:** There is no conflict of interest

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